REMARKS

Receipt of the Office Action mailed July 23, 2007 is acknowledged. Claims 1-22, 61, and 62 are pending. Claims 1, 8, 10 and 62 are amended; claims 9, 23-60 were previously canceled. Reconsideration in view of the above amendments and following remarks is respectfully requested.

Claim Rejections - 35 U.S.C § 103(a)-Kirpotin

The Examiner rejects claims 1-8, 10-22 and 61 under 35 U.S.C § 103(a) as being unpatentable over Kirpotin (U.S. Patent No. 6,110,491). Applicant has submitted a section 1.132 declaration of Pai Srikanth Annappa. Mr. Annappa, through his declaration, demonstrates:

(1) Kirpotin does not teach or suggest each and every element in the claimed invention (paragraphs 6 and 8);

(2) Kirpotin simply does not teach or suggest a process for the manufacture of long circulating non-pegylated liposomes as set forth in claim 1 (paragraph 7);

(3) unexpected results in that one of ordinary skill would not expect that by simply reducing the amount of hydration buffer, one would obtain a stable liposome without the need for PEG (paragraph 9);

(4) no one would be motivated to even consider Kirpotin for suggesting a nonpegylated liposome made by reducing the amount of hydration buffer (paragraph 10);

(5) the advantages in avoiding pegylation (paragraph 11); and

(6) the non-pegylated liposomes of the present invention are more effective in reducing tumor weight in comparison to pegylated liposomes (paragraph 12).

Accordingly, Applicant respectfully submits that Kirpotin does not teach or suggest each and every element of the claims and accordingly submits that claims 1-8, 10-22 and 61 are patentable under 35 U.S.C § 103(a). Applicant respectfully requests withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C § 103(a)-Forssen / Janoff

The Examiner rejects claims 1-8, 10-22 and 61-62 under 35 U.S.C § 103(a) as being unpatentable over Forssen (5,714,163) in combination with Janoff (4,880,635). Applicant respectfully contends that neither Forssen nor Janoff teach or suggest a process for the manufacture of long circulating non-pegylated liposomes as set forth in claim 1. Further, one skilled in the art would not be motivated to even consider Forssen or Janoff for suggesting a nonpegylated liposome made by reducing the amount of hydration buffer. Furthermore, the declaration of Mr. Annappa submitted contemporaneously herewith demonstrates unexpected results in that one of ordinary skill would not expect that by simply reducing the amount of hydration buffer, one would obtain a stable liposome without the need for PEG.

Accordingly, Applicant respectfully submits that Forssen and Janoff, alone or in combination, do not teach or suggest each and every element of the claims and accordingly submits that claims 1-8, 10-22 and 61-52 are patentable under 35 U.S.C § 103(a). Applicant respectfully requests withdrawal of this ground of rejection.

CONCLUSION

No additional fees are believed to be owed at this time. However, in the event that additional fees are required, the Commissioner is hereby authorized to charge Womble Carlyle Sandridge & Rice, PLLC Deposit Account No. 09-0528, or credit any overpayments to this account.

The Examiner is invited and encouraged to contact the undersigned at 703/394-2273 to discuss any matter in this application.

Respectfully submitted,
Womble Carlyle Sandridge & Rice, PLLC

Date: October 23, 2007

Teresa A. Lavenue
Registration No. 47,737
Phone: (703) 394-2273
Fax: (703) 790-2623

P.O. Box 7037
Atlanta, GA 30357-0037
Customer No.: 26158

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Daftary, et al.

Confirmation No.: 6940

Serial No.: 10/748,094

Examiner: Kishore, G.

Filed: December 31, 2003

For: Non-Pegylated Long-CirculatingLiposomes

DECLARATION UNDER 37 CFR §1.132

I, Pai Srikanth Annappa, do hereby declare and say as follows:

1. I have a masters degree in pharmacy from College of Pharmaceutical Sciences, Manipal, India. I currently hold the position of Senior Vice-President of Research and Development (Drug Delivery) for Bharat Serums and Vaccines Ltd.

2. I am a co-inventor on the following issued patents:
   a. Parenteral Cisplatin Emulsion (WO2001/007058)
   b. Clear Propofol Compositions (WO2002/45709)
   c. Amphotericin B Aqueous Composition (WO2002/069983)
   d. Amphotericin B Structured Emulsion (WO2000/197778)
   e. Clear Aqueous Anaesthetic Composition (WO2001/97796)
   f. Liquid Stable Composition of Oxazaphosphorine with Mesna (WO2004/022699)

g. Ifosfamide Compositions for Parenteral Administration and a Process for their Preparation (WO2004/050012)

h. Non-pegylated Long-circulating Liposomes (WO2004/058140)

i. Stable Emulsion Compositions for Intravenous Administration having Preservative Efficacy (WO2006/030450)

j. Intravenous Propofol Emulsion Compositions having Preservative Efficacy (WO2007/052288)

k. Aqueous Anaesthetic Compositions Comprising Propofol (WO2007/052295)

l. Propofol Emulsion Compositions for Intravenous Administration (PCT Appl.No. PCT/IN06/000466)

3. I have worked in the areas of developing parenteral products comprising liposomes, microspheres, intravenous emulsions/suspensions, phospholipid complexes, and soluble drug complexes.

4. I have reviewed and am familiar with the contents of the above-referenced patent application ("the present application") of which I am a co-inventor. I have also read the Office Action dated July 23, 2007 and the references cited therein. In particular, I have read U.S. Patent 6,110,491 (issued to Kirpotin and hereinafter referred to as "Kirpotin").

5. In the Office Action, the Examiner contends it is obvious to one of ordinary skill in the art to vary the amounts of the hydrating medium to obtain the best possible results. I respectfully disagree with this conclusion and my reasons are set forth below in the instant Declaration.

6. In summary, Kirpotin does not teach or suggest each and every element in the claimed invention. The novel liposomes of the present invention are made without polyethylene glycol (PEG), and the novel process of manufacture involves using a lower amount of hydration buffer than what was previously used to provide stable liposomes. Kirpotin does not teach non-pegylated liposomes nor does this reference

teach making the liposomes with a lower amount of hydration media. In addition, no one would even be motivated to make the present invention by reading Kirpotin, alone or in combination with the cited references, as the problems addressed by Kirpotin are different from the problems addressed by the present invention. The present invention concerns the manufacture of stable liposomes without using PEG (by using a smaller amount of hydration buffer) whereas Kirpotin tries to address issues surrounding liposome loading.

7. Kirpotin simply does not teach or suggest a process for the manufacture of long circulating non-pegylated liposomes as set forth in claim 1. In fact, Kirpotin teaches the preparation of liposomes containing polyethylene glycol (*i.e.* derivatized distearolphosphatidyl ethanolamine (PEG-DSPE)) to increase liposome stability (*see* Kirpotin's Examples 1 and 3-8).

8. Kirpotin also fails to teach or suggest an "aqueous hydration media used is in the range of 10 to 35 ml for each mmole of phospholipid present in the lipid solution" as recited in claim 1 of the present application. Based on my reading of Kirpotin, there is absolutely no teaching or suggestion to remove PEG and manufacture liposomes with a surprisingly low amount of hydration media. Further, it is my opinion that no one would one have thought to use such low amounts of hydration media to achieve a long lasting non-pegylated liposome upon reading Kirpotin (alone or in combination with the other cited references).

9. Furthermore, it was unexpected that by simply reducing the amount of hydration buffer, one would obtain a stable liposome without the need for PEG. The volume of aqueous hydration media as recited in claim 1 is less than what was previously known or considered an acceptable amount of aqueous hydration media. Thus, the volume of the aqueous hydration media as recited in claim 1 demonstrates a controlled reduction as compared to the amounts of hydration media used in conventional liposome and pegylated liposome manufacture. Surprisingly, we found that by reducing the volume of aqueous hydration media, and the composition of the

hydration media used, the toxicity of the doxorubicin loaded liposomes was reduced. Not bound by theory, we believe that the phospholipids were able to pack tighter together resulting in a thicker liposome membrane or "shell." The thicker "shell" provided for increased stability, long-circulation and slow release. The increased stability resulted in decreased toxicity without the need for PEG. The LD_{50} values of the different Doxorubicin compositions studied are provided Table 1 of page 7 of the published application. The LD_{50} dose was found to be 16.13 mg/kg whereas the LD_{50} dose for the marketed conventional preparation (ADRIAMYCIN) was 10.29 mg/kg. The LD_{50} for the marketed pegylated liposomal preparation CAELYX was 13.5 mg/kg. These results show that non-pegylated liposomes of the present invention have a reduced toxicity as compared to other Doxorubicin formulations and to pegylated-liposomal Doxorubicin formulations, and would be further devoid of hand foot syndrome associated with pegylation.

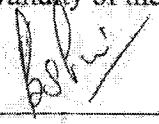
10. In my opinion, no one would be motivated to even consider Kirpotin for suggesting a nonpegylated liposome made by reducing the amount of hydration buffer as Kirpotin attempts to provide a solution to an entirely different problem from the problem addressed by the present invention. Kirpotin teaches methods of producing pegylated (PEG) liposomes in an effort to increase encapsulation efficiency. In other words, Kirpotin is concerned with methods of increasing the loading of the liposomes. Thus, the invention taught by Kirpotin and the present claimed invention are aimed at solving two entirely different problems.

11. In contrast to Kirpotin, the present invention is concerned with making liposomes without the use of PEG. The present invention is directed to non-pegylated liposomes and methods of their manufacture to avoid the occurrence of "Hand-Foot syndrome," associated with preparations containing pegylated phospholipids. *See* present published application, para. 0013. Additional advantages in avoiding pegylation are also illustrated in Table 1 on page 7 of the published application. Table 1 shows that non-pegylated doxorubicin liposomes of the present invention have lower toxicity than conventional pegylated liposomes.

12. Furthermore, the non-pegylated liposomes of the present invention have been shown to be more effective in reducing tumor weight in comparison to pegylated liposomes. The test results summarized in Table 2 support this position. Specifically, the difference in tumor weight and effectiveness was measured by T/C % (test to control percentage). In this study (Example VI), the highest ratio of T/C using CAELYX was -78 at 12 mg/kg and -34.7 at 6 mg/kg, whereas when using the non-pegylated doxorubicin liposomes of the present invention, the highest was -93.4 at 12 mg/kg and -89.43 at 6 mg/kg. These results demonstrate that the non-pegylated doxorubicin liposomal compositions of the present invention are more effective in reducing tumor weight than the currently marketed pegylated liposomal formulation.

13. In conclusion, it is my opinion that the present invention would not be obvious light of Kirpotin, alone, or in combination of the cited references.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Pai Srikanth Annappa

Date: October 18, 2007